REMARKS

Status of the Claims.

Claims 1-22 are pending with entry of this amendment.

Claim 1 is amended herein without prejudice and is not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record. The amendment introduces no new matter and support is replete throughout the specification. For example, in claim 1 the terms "specified" and "different" are added to describe the transcription factors and the reporter sequences to which they correspond. Support for this amendment is found, e.g., on page 16, line 13, to page 17, line 25, describing the correlation of a different reporter sequence with each particular cis element/transcription factor pair. Examples of such pairings are also provided in Figure 2.

Claims 1-22 were rejected for alleged obviousness. Applicants traverse all rejections for the reasons of record, and, additionally, for the reasons noted herein.

THE CLAIMS ARE NOT OBVIOUS OVER KAUFFMAN IN VIEW OF MORRIS

The Examiner rejects claims 1-22 under 35 U.S.C. §103(a) for alleged obviousness over Kauffman in view of Morris. Applicants traverse.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure. M.P.E.P. §2143.

The Examiner alleges that Kauffman and Morris teach a library of nucleic acid constructs as claimed and that because both references address expression methods and a need for high throughput methods it was obvious to combine them to produce the claimed invention. However, this argument does not recognize the fact that **each** construct in the claimed library comprises a known cis element that recognizes and binds to a specified transcription factor and that each construct comprises two coordinated variable regions: each

cis element/transcription factor pair corresponds to a different reporter sequence. Therefore the claims are not obvious over Kauffman and Morris. Each of these elements is discussed in detail below.

The references do not teach every element of the claims

The first requirement of establishing a case for obviousness is that *all of the claim limitations must be taught by the combination of references*. MPEP 2143.03. The rejection alleges that each and every limitation of the claims is provided by either Kauffman or Morris. In fact, given that the references, alone or in combination, provide no information at all regarding any specific transcription factors or the particular cis acting sequences to which they bind, it is quite apparent that the combination of references is completely insufficient to provide the elements of the claimed invention. Although Kauffman discusses cis elements and transcription factors, it gives no indication regarding how to **identify** and **select** a group of cis elements, each of which binds a specified transcription factor.

The Examiner alleges that Kauffman teaches cis acting nucleic acid elements that bind transcription factors, wherein there is a sequence variation within the cis element sequence, and a reporter sequence that corresponds to the cis element sequence. The rejection relies on Morris for the teaching that the reporter sequence varies within the library. Applicants respectfully disagree for the reasons set forth below.

For a teaching regarding cis elements that bind to specified transcription factors, the rejection points to claim 38 of Kaufman, which is drawn to a plurality of nucleic acids that comprise cis acting nucleic acid elements, and page 1, lines 29-30, giving an example of transcription factors as one type of molecule that binds a cis acting nucleic acid element. While admittedly, the reference discusses cis element sequences and binding of transcription factors to those sequences, the reference does not teach cis element sequences that bind to specified transcription factors. In addition, the reference does not provide a library of nucleic acid constructs in which **each** of the constructs binds to a transcription factor as claimed. Kauffman explicitly defines, on page 14, line 20, to page 15, line 2, nucleic acid binding factors to be molecules that bind cis acting nucleic acid elements and states that the group of possible binding factors includes not only transcription factors, but

also replication factors, translation factors, restriction and modifying factors, structural and assembly factors, and the like. Because the cis acting sequences of Kauffman include sequences that bind to things other than transcription factors and the claimed invention comprises a library of constructs wherein every construct binds to a transcription factor, Kauffman does not teach every element of the claimed invention. In addition, the cis acting sequences in the claimed invention bind to **specified**, e.g., named or explicitly stated, transcription factors. Therefore, the references cited do not teach every element of the claimed invention and cannot render the claimed invention obvious.

Previous arguments over this teaching have focused on the assertion that the constructs of Kauffman inherently include all the constructs of the present invention because Kauffman includes 10^{13} different sequences of the appropriate length and would therefore include every cis element that binds to every transcription factor. These 10^{13} sequences are **potential** cis element sequences and no teaching is provided in Kauffman regarding how to identify and select those sequences that would be included in a library as claimed, e.g., a library in which **every** sequence binds a specified transcription factor. According to the Federal Circuit in *In re Newell,* reliance on an alleged inherent teaching is not sufficient to support an obvious rejection. "A retrospective view of inherency is not a substitute for some teaching or suggestion that supports the selection and use of the elements in the particular claimed combination. In deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art; for that which may be inherent is not necessarily known, and obviousness cannot be predicated on what is unknown." See, *In re Newell*, 891 F.2d 899, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir. 1989). A teaching that a nucleic acid between 5 and 20 nucleotides in length of any combination of naturally occurring nucleotides, while technically including every possible nucleic acid of that length, is not sufficient to teach a particular subset of nucleic acids because it does not teach how to identify and select that subset, e.g., a group of cis acting sequences that each bind to a specified transcription factor as required in the claimed invention. So even if the claimed nucleic acid constructs are all inherently included in the nucleic acids of Kauffman, there is no teaching regarding how to select and identify the cis acting sequences and the transcription factors to which they bind.

Therefore, the cited reference does not teach each and every element of the claimed invention and cannot render it obvious.

The Examiner further alleges that the Kauffman nucleic acids comprise a corresponding reporter for each cis acting element. For this allegation, the rejection refers to pages 14 and 19 of Kauffman, describing the use of a detectable moiety on a nucleic acid. The rejection takes the term "correspond" to mean merely that a reporter exists in the nucleic acid sequence. In Kauffman, "detectably tagged" refers to a means to show whether a nucleic acid element is unbound or bound, e.g., whether it is a cis element bound to a protein or not a cis element at all; it merely detects the presence or absence of an unidentified cis element sequence. This detectable element is not a corresponding reporter in the sense of the claimed invention; it does not correspond to a particular cis-element. For example, in the claimed invention, each cis element recognizes a specific transcription factor and each cis element corresponds to a different reporter, thereby allowing the identification of a specific cis element/transcription factor pair when the reporter is detected. Kauffman does not teach a plurality of cis elements each corresponding to a different reporter sequence as claimed; all the detectable tags in Kauffman are identical to each other and can merely detect the presence of a cis acting element, not a particular cis element; there is no correspondence. They cannot tell the user which particular cis acting sequence is present because they are not correlated to the cis acting sequence, i.e., they do not "correspond" to a particular cis acting sequence as presently claimed. There is no correspondence, e.g., association or relation, between particular cis acting sequences and reporter sequences in Kauffman and **cannot be** because the cis acting sequences are not known and identified as they are in the present invention, e.g., wherein each cis element sequence is associated with a **specified** transcription factor and each cis element/transcription factor pair is specifically associated with a **different** reporter sequence. Therefore, the references do not teach every element of the claimed invention.

The rejection relies on Morris to teach the second variable region in the nucleic acid constructs of the claimed invention, because clearly, the nucleic acids in Kauffman do not contain two corresponding variable regions. Morris does not teach two corresponding variable sequences any more than Kauffman does. Morris, if anything,

teaches a variable nucleic acid tag that hybridizes to another nucleic acid. To teach every element of the claimed invention, the references must teach a single nucleic acid construct comprising **two corresponding variable regions**. The fact that one reference has a variable region in one nucleic acid and another reference teaches a variable region in an unrelated nucleic acid, both of which are used in different ways cannot be combined to produce one nucleic acid with two variable regions that vary dependently or correspond to each other as claimed, e.g., to allow identification of cis acting elements and transcription factors. Neither reference teaches the addition of a variable reporter to a nucleic acid that already has a variable cis element region. The cited references in combination do not teach each and every element of the claims and the rejection must be withdrawn.

Finally, Applicant would like to call attention to the invention "as a whole" concept. As pointed out by the Federal Circuit, "the invention must be viewed as a whole." See *Bausch & Lomb, Inc., v. Barnes-hind/Hydrocurve, Inc.,* 796 F.2d 443 (Fed Circuit 1986). When viewed as a whole, the claimed invention comprises a library of nucleic acids wherein each nucleic acid comprises two variable regions, a cis element that binds to a specific transcription factor and a unique reporter that corresponds to each cis element. Nowhere in the prior art has such a combination been shown or suggested. Even if variable regions, transcription factors and cis element sequences have been shown individually, nothing in the cited references considers the concept of a single nucleic acid with these two corresponding variable regions. The whole concept of the claimed invention must be considered when showing obviousness and it is clear that the cited references, alone or in combination, have not suggested this concept. Therefore the claimed invention is not obvious over Kauffman and Morris

In summary, Kauffman and Morris in combination do not teach a library of nucleic acid constructs, wherein **each** construct comprises a different cis element sequence, wherein each cis element sequence binds to a specified, i.e., known, transcription factor, and each cis element sequence corresponds to a different reporter element. Therefore, the combined references, Kauffman and Morris, do not teach every element of the claimed invention and cannot render the claimed invention obvious.

No specific motivation to combine Kauffman and Morris exists in the prior art.

In addition to the obvious failure to teach every element of the claimed invention, no *particular* motivation exists for combining Kauffman and Morris. As set forth in the MPEP, "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP 2143.01. As the Courts have clearly stated, this means that the Patent Office "must explain why one of ordinary skill in the art would have been motivated to select references and to combine them to render a claimed invention obvious."

There is nothing in Kauffman or Morris to suggest or motivate the combination of references at issue - at most, the Examiner's allegation is that Kauffman and Morris both pertain to expression methods and the need to automate detection. Any possible suggestion that the Kauffman nucleic acids *in particular* would benefit from the tags in Morris would not result in a library of nucleic acids as presently claimed.

The Examiner relies on a quote in Kauffman stating that, "nucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures **for identifying cis-acting nucleic acid elements**." (emphasis added). The claimed invention is not about "identifying cis acting nucleic acid elements." Therefore, the quote cannot provide a motivation to produce the claimed invention. If anything, the quote provides a motivation to automate the detection for a library of probes for identifying cis acting nucleic acid elements. The claimed libraries comprise previously identified cis acting elements that bind to specified transcription factors, e.g., for identifying when those specified transcription factors are present in a cell sample or with what other factors the specified transcription factors are interacting. Therefore, whatever motivation is espoused by Kauffman is meaningless to the claimed invention. It motivates, if anything, a change in a procedure that is irrelevant to the present claims, e.g., the search for cis acting elements. The aims of Kauffman and those of the claimed invention are not identical and therefore any suggestions regarding improvements to Kauffman are irrelevant to the claimed invention.

Another motivation alleged for combining Morris and Kauffman is to make a more efficient process, e.g., by reducing "ambiguities in the interpretation of hybridization results" by reducing unwanted hybridization between probes. Applicants question whether the more efficient process motivated by this statement is a process as described in Kauffman or a process as described in Morris. The suggestion must come from the references (or at least the prior art) and not simply from the present application. Kauffman describes a process of identifying previously unidentified or unknown cis element sequences; Morris describes a nucleic acid hybridization process; and the present application claims a library for use in identifying transcription factors. The claims are not drawn to a process, so again Applicants question whether the motivation put forth in the rejection regarding a more efficient *process* is even relevant to the claimed invention, especially given that *the claimed nucleic acid libraries would have no use in either of the processes described in the two references*. Therefore, the motivation to make a more efficient method of finding cis-elements does not provide a motivation for combining Kauffman and Morris to achieve the claimed invention

Furthermore, there is no suggestion or motivation in Morris or Kauffman to provide a second variable region in a nucleic acid construct such that the two variable regions correspond to a particular combination of molecules. The rationale behind the variable sequences in Morris, e.g., greater efficiency, is meaningless in the context of the claimed invention because the claimed invention uses a variable sequence to correlate a detectable moiety to a cis element/transcription factor pair, e.g., for identification purposes. Given the goals and issues that Kauffman and Morris describe, there is no motivation to combine them in the manner alleged to produce a library of nucleic acids as claimed.

The last allegation regarding motivation to combine is that the two references are both drawn to "expression" methods for use in the creation of nucleic acid libraries. This does not provide a sufficient or particular motivation to combine these two specific references. For example, what specific motivation would lead someone to select these two references from the 34,272 patents that turn up in a US patent search for the terms "expression" and "library". Many references exist relating to expression, nucleic acid chips, and nucleic acid libraries. Without a more specific motivation, it is not clear what would

lead one skilled in the art to select these two particular references out of the thousands available. In particular, neither of these references involves the identification of transcription factors, so why would anyone skilled in the art look at these references and be motivated to create a specific library as claimed, e.g., a comprising two corresponding variable regions for identification of transcription factors?

Finally with regard to motivation to combine, the Examiner has not stated *how* the combination of references is even to be achieved. No teaching regarding how to identify or select a group of nucleic acids that specifically recognize and bind to specified, e.g., specific known or named, transcription factors is provided by Kauffman or Morris. It is completely unclear even how the various protocols of Morris are to provide a nucleic acid construct that correlates a particular transcription factor with a particular reporter, e.g., for use in the identification of transcription factor interactions. If the Examiner cannot set forth (without reference to the present application) *how* the combination is to be achieved, there is just no rational way that the combination can be considered obvious.

No expectation of success exists for the combined references to produce the libraries as presently claimed.

In short, the combination of Kauffman and Morris completely fails to establish a case for obviousness. The combination of references does not even remotely provide the limitations of the claims; there is no *specific* motivation to make the combination of references supposed, and there was, plainly, no expectation that the nucleic acids of Kauffman combined with the techniques of Morris could result in libraries as claimed, prior to Applicants' invention. Applicants ask a simple question: which of the 10^{13} sequences of Kauffman are to be used with the reporters of Morris to provide a library specific to transcription factors as claimed? A library comprised of the 10^{13} sequences of Kauffman would not be a very efficient library for the identification of transcription factors and no teaching or suggestion is provided for how to select those members of the group that would make a successful library for such a use. Therefore, no expectation of success is provided in the references for the nucleic acids of Kauffman and the variable tags of Morris to work as

do the libraries of the claimed invention. The rejection completely fails to state a case for obviousness and must be withdrawn.

THE CLAIMS ARE NOT OBVIOUS OVER LI IN VIEW OF MORRIS

Claims 1-22 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Li in view of Morris. Applicants traverse.

As discussed above, three requirements must be met for a *prima facie* case of obviousness. Specifically, a *prima facie* case of obviousness requires that the combination of the cited art, taken with the general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. In re Geiger, 815 USPQ2s 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection the cited references must additionally provide a reasonable expectation of success. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991), citing In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). As described in detail below, the three requirements are not met for this rejection and the rejection must be withdrawn.

The references do not teach every element of the claims

The Li reference contains different cis elements constructs comprising promoters and reporters. However, as admitted in the rejection, there is no library of constructs in Li wherein each nucleic acid comprises two variable sequences that vary dependently with each other. Although different reporters exist and different cis-elements exist, there is no teaching or suggestion regarding a combination of these constructs as presently claimed, wherein each cis-element sequence has a different reporter that corresponds to a particular cis element/transcription factor pair. The rejection again relies on Morris for the teaching regarding a variable reporter, but Morris suffers the same defects here as above. Morris does not teach adding a second variable sequence to a nucleic acid comprising a first variable sequence, wherein the two variable sequences vary dependently.

The combined references do not teach every element of the claimed invention because neither reference teaches a single nucleic acid construct with two variable elements that correspond to each other – a cis element and a reporter. The correspondence element is

lacking in both references, alone or in combination. As evidence of a supposed correspondence between a reporter and a cis element the Examiner states that the amount of reporter activity in Li shown to correspond to the **type** of cis element. Applicants respectfully disagree. The reporter activity in Li corresponds to the presence or absence of a cis element; it gives no information regarding the type of cis element present because no correspondence or association exists between a particular cis element and a reporter.

Further, neither reference teaches a library of nucleic acids constructs comprising cis elements as claimed. Although there are multiple possible definitions for the term "library," they all allude to some type of collection, e.g., all in a cell sample when considering medical and biological definitions. However, the alleged library of Li merely comprises multiple individual nucleic acids constructs, e.g., that can be individually transfected into a cell. The individual constructs do not form a collection, nor was any suggestion made in the prior art that they would be used together as a collection or library, e.g., transfected into a cell sample. No correspondence between a reporter and a specified cis element/transcription factor pair as claimed can be found in these individual constructs. Therefore, the cited references do not teach every element of the claimed invention and cannot render it obvious.

No specific motivation to combine Li and Morris exists in the prior art.

As the Court stated with respect to the type of motivation evidence that must be presented by the Office, "Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination **in the manner claimed.**" In Re Lee 61 USPQ 1430 at 1433, (Fed Cir. 2002), *citations omitted.* This requirement for particularity in the rejection is the counterbalance to simply making a raw hindsight reconstruction argument, in which the Examiner simply restates a *benefit* provided by an Applicant's invention (e.g., a library comprising nucleic acids probes with corresponding variable regions that allow identification of interactions between different transcription factors or simultaneous identification of multiple transcription factors) as the *motivation* for the asserted combination. This type of rationale is the rawest form of improper hindsight reconstruction of the invention.

The motivation to combine the references is lacking in this rejection as in the above argument. Part of the inventive concept presently claimed is putting two variable sequences (a cis element and a reporter) on the same nucleic acid construct and having them correspond to each other, e.g., within the same library of constructs such that the multiple transcription factors could be identified in the same sample. Only a hindsight argument using the present claim as a blueprint can take a variable sequence in one application and combine it with an unrelated individual construct in a totally different application and construct the nucleic acids of the present invention. **There is no suggestion to put these two particular variable sequences into the one nucleic acid construct except in the present application.**

The particular motivation espoused by the rejection is that both references involve expression and cloning and so does the claimed invention. The Examiner relies on a statement from the summary of invention in Li regarding "detecting expression of a reporter gene" (quoted from page 19 of the rejection) as an argument that both Li and Morris involve expression and therefore one of skill would be motivated to combine them. However, Applicants respectfully point out that when expression of the reporter gene is used as a detection method, in Li and in the claimed invention, then the hybridizing probes of Morris are irrelevant. Therefore, one would not be motivated by this statement in Li to combine the nucleic acids of Li and the improved hybridization techniques of Morris into the claimed invention. Without a more particular and accurate motivation, the rejection must be withdrawn.

No expectation of success exists for the combined references to produce the libraries as presently claimed.

Finally, the expectation of success has not been shown for the combination of Li and Morris to produce the nucleic acid constructs of the claimed invention. The rejection has not stated how the two unrelated variable sequences would be combined to form a library of nucleic acid transcription factor probes as claimed. Therefore, the rejection must be withdrawn.

CONCLUSION AND REQUEST FOR EXAMINER INTERVIEW WITH SUPERVISING EXAMINER

The claims are in condition for allowance. A notice of allowance at an early date is, therefore respectfully requested. In the event that any issues of substance are believed to remain, Applicants respectfully request an Examiner Interview with Examiner Epperson and a Supervising Patent Examiner.

If the claims are deemed not to be in condition for allowance after consideration of this Response, please telephone the undersigned at (510) 337-7871 to schedule an interview.

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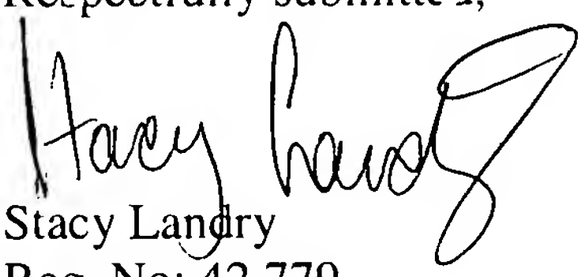
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for **3** months;
2) A transmittal sheet;
3) A receipt indication postcard.